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ADMIN PROCEEDINGS STAFF

U. S. Department of Health and Human Services
Dockets Management Branch (HFA 305), Room 4-62
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Docket Number 76N-052N (Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for OTC Nasal Decongestant Drug Products)

Gentlemen:

In the Federal Register of January 15, 1985, the FDA published a Notice of Proposed Rulemaking under 21 CFR Part 341, establishing a Tentative Final Monograph identifying conditions under which Over-the-Counter Nasal Decongestant products are generally recognized as safe and effective and not misbranded. The Proposed Regulation included labeling indications and dosage directions under 21 CFR 341.80 (b) and (d), which are the subject of the comments presented below.

1. Labeling "Exclusivity Policy"

McNeil Consumer Products Company believes that FDA should not prescribe exclusive lists of terms from which labeling indications must be drawn. Rather than prohibiting the use of alternative truthful terminology, FDA should permit manufacturers to choose consumer oriented language to communicate the desired label indications, so long as such language is not false or misleading.

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It is noted that FDA proposed certain revisions to the "Exclusivity Policy" on April 22, 1985 and McNeil will submit comments on that proposal separately.

2. Indications for Use [341.80(b)]

The Tentative Final Monograph for OTC Nasal Decongestants calls for all products containing decongestant active ingredients to carry label indications limited to the phrase "For the temporary relief of nasal congestion due to the common cold (cold), hay fever (allergic rhinitis) or other upper respiratory allergies or associated with sinusitis." McNeil believes that it is inappropriate to require all three of the above indications for all products containing oral nasal decongestants.

The consumer audiences to whom products for the treatment of the common cold, allergy and sinusitis are entirely different. The use of all three indications for all products containing oral nasal decongestants may not only be extraneous, but potentially confusing to consumers. This is particularly true for combination cold products which may be totally inappropriate for persons suffering allergy or sinusitis.

McNeil therefore requests that the indications section of the TFM be amended to allow manufacturers to choose from among any of the three indications noted above, as appropriate for the consumer market segment to which the product is directed [i.e.: either the common cold (cold), allergy or sinusitus]. Accordingly, it is requested that 21 CFR 341.80(b)(1) be modified to read:

"The labeling of the product contains a statement of the indications under the heading "Indications" which includes one or more of the following indications:

"For the temporary relief of nasal congestion due to (select one of the following) the common cold (cold), hay fever (allergic rhinitis) or associated with sinusitis."

Other Allowable Indications [341.80(b)(2)]

To permit meaningful alternate consumer oriented label indications, the "other allowable Indications" given in the TFM should be available as alternative statements rather than in addition to those permitted under 341.80(b)(1) above.

McNeil also believes that the underlined terms below are synonymous with those already included in 341.80(b)(2) and since they are consumer oriented terms, should also be permitted, e.g. "temporarily relieves stuffed-up head (stuffy head). Therefore, McNeil requests that 21 CFR 341.80 (b)(2)(i) be modified to read:

"(2) Other allowable indications. As an alternative to the indications listed in 341.80(b)(1) above, the labeling of the product may contain any of the following statements:

(i) For the temporary relief of (select one of the following): stuffy nose, stopped-up nose, nasal stuffiness, clogged-up nose, stuffed-up head, stuffy head."

3. Warnings [341.72(c)]

The current FDA mandated warning language tends to read like a medical text and also contains redundant and in some cases inappropriate warning language. For example, the TFM calls for a drug interaction precautionary statement for adults and children which essentially duplicates statements required in other warnings. Therefore, McNeil requests that 21 CFR 341.80(c)(1)(i)(c) be modified to read as given below and that 341.80 (c)(1)(i)(d) be eliminated:

> (c)" Do not take this product if you are being treated for heart disease, depression, high blood pressure, thyroid disease, diabetes, or have difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

Similarly for products labeled for children under age 12, it is requested that 21 CFR 341.80(c)(1)(ii)(c) be modified as outlined below and 341.80(c)(1)(ii)(d) be eliminated:

> (c) "Do not give this product to children who are being treated for heart disease, thyroid disease, diabetes, high blood pressure or depression unless directed by a doctor."

4. Labeling [341.80(d)]

Recommendations for Changes in Pediatric Dosage Schedules

McNeil Consumer Products Company's recommends the following changes be made in the pediatric dosing schedules used in the "Directions" section [341.72 (d)] of the monograph:

A. Addition of an optional dosage schedule which utilizes the concept of a pediatric dosage unit equivalent to 1/8 the adult dose and includes additional age groupings developed to better utilize the pediatric dosing unit concept; and

B. Addition of a weight-based schedule that could be incorporated on an optional basis as part of the dosing recommendations in consumer package labeling.

C. Addition of a professional dosage schedule for children under 2 years of age.

Recommendation: New pediatric dosing schedule based on more finely divided age breaks.

Most cough-cold products currently available in the nonprescription market are targeted toward either adult or pediatric patients. For products primarily intended for pediatric use, there is a need for a dosing schedule that would provide for administration of incremental doses to the pediatric patient through his/her growing years.

Adoption of a dosing system similar to that used in the Proposed Monograph for OTC Internal Analgesic Drug Products (1) and reported in the published literature (2, 3) would provide consistency between various monographs and would allow for consistency in the formulation of combination products. For products targeted for adults, which also provide dosage recommendations for the pediatric patient, it is reasonable to continue to allow the option of using dosing schedule currently in the Tentative Final Monograph.

The Pediatric Dosing Unit (PDU) concept. Using a relatively standardized pediatric dosing unit (PDU) as the basis, pediatric dosing schedules can be developed that are consistent with the need of the growing pediatric patient by using incremental age and weight ranges consistent with the typical growth pattern in children. In addition, the PDU concept allows products intended for oral administration with relatively fixed dosing increments to be administered safely and effectively.

Importantly, the PDU dosing system can be used for essentially all orally administered over-the-counter preparations intended for pediatric use. Because it is based on standard weight ranges and fractions of a recognized adult dose, it can be applied to any drug category or specific ingredient.

The standard pediatric dosing unit concept can be applied independent of drug half-life or dosing intervals, as long as dosing intervals can be adjusted to take into account drug elimination rates.

The most appropriate pediatric dosing unit is one-eighth of the usual adult dose. Other fractions of adult doses, such as one-twelfth, one-tenth, or one-fifth, have been evaluated, but do not meet the needs for pediatric formulations as satisfactorily. Using a PDU that is one-eighth of the usual adult dose, a dosing framework can be developed with seven incremental age periods and/or seven incremental weight ranges. In addition, a PDU that is one-eighth of the usual adult dose is consistent with the pediatric dosing unit already in use with acetaminophen and aspirin products and the incremental age-breaks are consistent with the Proposed Monograph for Internal Analgesic Drug Products.

Application of the pediatric dosing unit concept to consumer labeling. For products whose labeling is limited to children 2 years and older, only five age breaks would be incorporated into package labeling. Additional professional labeling also could be developed for the younger age child if desired. (see below)

The following summarizes the recommended age periods and the number of pediatric dosing units that would be required at a given age to maintain constant, incremental dosing throughout the pediatric age period:

RECOMMENDED PEDIATRIC DOSING SCHEDULE

Age Ranges (years)	Number of Pediatric Dosing Units (PDUs) for that Age Range
11	6
9-10	5
6-8	4
4-5	3
2-3	2

Note: Eight PDUs would be the equivalent of the usual adult dose. For children under two years, see professional labeling recommendations.

The following compares the age groupings for the PDU schedule with the age groups in the Tentative Final Monograph showing the age breaks and relative doses as fractions of the adult dose for each of the specific age ranges.

COMPARATIVE AGE GROUPINGS FOR PROPOSED PDU DOSING SCHEDULE AND TENTATIVE FINAL MONOGRAPH SCHEDULE WITH DOSES DISPLAYED AS FRACTIONS OF THE USUAL ADULT DOSE.

Age (years)	Fractional Dose Administered PDU Schedule	TFM Schedule
Adult	1.0	1.0
11	0.75	0.50
10	0.625	"
9	"	"
8	0.50	"
7	"	"
6	"	"
5	0.375	0.25*
4	"	"
3	0.25	"
2	"	"

*Professional labeling.

Applicability of this approach across various drug (monograph) categories. To demonstrate the utility of this approach, we have applied this concept to four drug compounds: acetaminophen, chlorpheniramine, dextromethorphan, and pseudoephedrine.

Using the PDU system, pediatric dosing units can be identified, mg/kg dosing ranges calculated, and dosing schedules established. For acetaminophen, the pediatric dosing unit would be 80 mg and would produce a dosing schedule that would result in a dosing range of 10 to 15 mg/kg per dose. For chlorpheniramine, the pediatric dosing unit would be 0.5 mg, with a dosing range of 0.6 to 0.10 mg/kg. For dextromethorphan, the pediatric dosing unit would be 2.5 mg, with a dosing range of 0.3 to 0.5 mg/kg. For pseudoe- phedrine, the pediatric dosing unit would be 7.5 mg, with a dosing range of approximately 1.0 to 1.5 mg/kg. Appendix A contains complete dosing schedules for these four agents using the PDU system.

To further illustrate this, Appendix B (Figure 1) compares the proposed PDU dosing schedule with the already approved TFM dosing schedule. This comparison illustrates dose/weight ratios for specific ages, based on 50th percentile weights for age. The comparison arbitrarily sets at unity the mg/kg dose/weight ratio calculated for ages 6 and 12, based on the TFM doses for children 6 and 12 years of age. As the figure demonstrates, the PDU schedule, by using narrower age ranges with a greater number of incremental breaks, produces a result in which the lowest single doses are between 70 and 75% of the index doses, with no single dose exceeding that of the index doses. The single doses we recommend do not exceed the maximum single doses in the Tentative Final Monograph on a mg/kg basis, yet provide greater consistency of dosing in an effective therapeutic range.

Applicability of this approach to all Category I oral nasal decongestants. This approach can be applied to all Category I Nasal Decongestants. Appendix C summarizes the dosing recommendations for all oral nasal decongestants included as Category I ingredients in the TFM. As can be seen, a reasonable dosing schedule can be established for each Category I oral nasal decongestant.

In summary, we have provided data supporting the utility of a new pediatric dosing schedule that incorporates additional age breaks consistent with those provided in the Proposed Monograph for Internal Analgesic Drug Products.

We also have reviewed the application of this dosing to four drugs from four different monographs and to the entire list of Category I oral nasal decongestants, demonstrating that this is a rational and consistent approach to the dosing of nonprescription medications in the pediatric patient. This approach incorporates the concept of a standard pediatric dosing unit (PDU) that is one-eighth the standard adult dose with age increments of 2-3, 4-5, 6-8, 9-10, and 11 years.

Recommendation: Weight Based Dosing Schedule

There is an additional benefit consumers to have available an optional weight related dosing schedule on package labels. Such schedules can be used with children when weight is known, and is especially useful when children are very large or very small for their age and when children approach the usual age breaks for a given dosing schedule. While dosing of drugs in the pediatric patient has been recommended on the basis of age, weight, and body surface area, and while each of these parameters can be interrelated, there are some specific preferences for each approach.

While body surface area may reflect more accurately the magnitude of change that occurs in the growing child, body surface area is not a growth parameter that is in common use in the pediatricians' offices and is clearly not a parameter that is used by parents. As a result, the use of weight as a parameter for dosing of drugs has far more practical merit. Weight changes are reasonably similar to the changes in body surface area and thus, dosing by weight is a reasonable substitute for dosing by body surface area.

While age has the advantage that it is almost universally known and is the simplest parameter for consumer use, and while age can be used as a reasonable guide to growth in the child provided one takes into consideration the wide variations in growth that occur, a weight-based dosing schedule offers a significant benefit for those consumers or health professionals who would like to dose by weight. Since weight is not always known, we would recommend that the weight-based schedule be optional.

Recommended Weight Schedule. In order to avoid unnecessary consumer and health professional confusion when weight-based schedules are made available, we recommend that standardized weight ranges be adopted. Our review indicates that increments of 12 pounds are the most consistent with the pediatric dosing unit concept. There are currently in use other weight schedules that deviate by a few pounds from that proposed herein, but the simplicity of 12 pound increments and its consistency with the age breaks incorporated in the pediatric dosing unit concept make it ideal. We recommend that the following weight schedule be utilized:

RECOMMENDED WEIGHT-BASED DOSING SCHEDULE

Weight Ranges (pounds)	(kilograms)	Number of Pediatric Dosing Units (PDUs) for that Weight Range
72-95	33.0-43.9	6
60-71	27.0-32.9	5
48-59	22.0-26.9	4
36-47	16.0-21.9	3
24-35	11.0-15.9	2

Because weight is still measured and remembered by the average parent in the United States in pounds, the proposed schedule is in pounds, with kilograms included as an alternate. Appendix B (Figure 2) demonstrates the consistency of dosing that occurs when these weight ranges are used.

Recommendation: Professional Dosage Schedule for Children Under Age 2:

In order to provide additional assistance to professionals seeking guidance about dosing of nasal decongestants, we would recommend that a professional dosage schedule be adopted for children under age 2 years based on the PDU system. The schedule would be as follows:

Age	No. PDUs
1 yr	1.5
4-11 mo	1.0

This can be adapted readily to any appropriate nasal decongestant. For example, for pseudoephedrine, the Professional Labeling section would be amended to read as follows:

> Children one year of age, 11.25 mg every 4 to 6 hours, not to exceed 45 mg in 24 hours; children 4 months to under 1 year, 7.5 mg every 4 to 6 hours, not to exceed 30 mg in 24 hours.

Adoption of such a professional dosage schedule would be of great benefit to the health professional.

Summary of Recommendations on Directions:

In summary, McNeil Consumer Products Company is making three recommendations with regard to changes in the directions for pediatric dosing of nasal decongestants:

1. We recommend that FDA add to consumer package labeling directions an optional pediatric dosing schedule, based on the concept of a standard pediatric dosing unit, that provides an increased number of incremental age breaks, 2-3, 4-5, 6-8, 9-10, and 11 years; and

2. We recommend that FDA add to consumer package labeling directions an optional weight schedule, consistent with the newly proposed age-related schedule, as summarized herein.

3. We recommend that FDA add to the oral nasal decongestant TFM a schedule of professional dosage for children below age two.

Sincerely,
MCNEIL CONSUMER PRODUCTS COMPANY

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REFERENCES

1. Proposed Monograph For OTC Internal Analgesic, Antipyretic and Antirheumatic Products, Federal Register 42:35346-494, 1977.

2. Done, A.K., Yaffe, S.J., and Clayton, J.M.: "Aspirin dosage for infants and children" J. Pediatrics 95:617-625, 1979.

3. Temple, A.R.: "Pediatric dosing of acetaminophen" Pediatric Pharmacology 3:321-327, 1983.

APPENDIX A. PEDIATRIC DOSING UNIT DOSING SCHEDULE AS APPLIED TO ACETAMINOPHEN, CHLORPHENIRAMINE, DEXTROMETHORPHAN, AND PSEUDOEPHEDRINE.

General PDU Dosing Schedule

Age (years)	No. PDUs
11	6
9-10	5
6-8	4
4-5	3
2-3	2
1	1.5
4-11 mo.	1

Pediatric Dosing Unit dosing schedule for acetaminophen, chlorpheniramine, dextromethorphan and pseudoephedrine.

	Acetaminophen	Chlorpheniramine	Dextromethorphan	Pseudoephedrine
"Usual" adult dose:	650-1000 mg	4.0 mg	20 mg	60 mg
Pediatric dosing unit:	80 mg	0.5 mg	2.5 mg	7.5 mg
Dosing Schedule				
11 yrs	480 mg	3.0 mg	15.0 mg	45.0 mg
9-10 yrs	400 mg	2.5 mg	12.5 mg	37.5 mg
6-8 yrs	320 mg	2.0 mg	10.0 mg	30.0 mg
4-5 yrs	240 mg	1.5 mg	7.5 mg	22.5 mg
2-3 yrs	160 mg	1.0 mg	5.0 mg	15.0 mg
1 yr	120 mg	0.75 mg	3.75 mg	11.25 mg
4-11 mo.	80 mg	0.5 mg	2.5 mg	7.5 mg
Dosage:				
Approximate mean:	12.5 mg/kg	0.08 mg/kg	0.4 mg/kg	1.25 mg/kg
Approximate range:	10-15 mg/kg	.065-.095 mg/kg	0.3-0.5 mg/kg	1.0-1.5 mg/kg